PATENT SPECIFICATION

NO DRAWINGS

1,101,108

1,101,108

D2

Date of Application and filing Complete Specification: Dec. 2, 1966.
No. 53974/66.
Application made in Germany (No. B84851 IVd/12p) on Dec. 6, 1965.
Complete Specification Published: Jan. 31, 1968.

SEE ERRATA SLIP ATTACHED

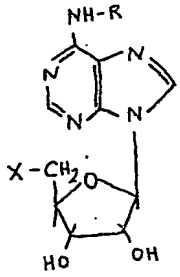
Index at acceptance: —C2 C(1F2C5, 1F2D3, 2D7, 2D19, LE32Y, LE36Y, LE45Y, LE200, LE214, LE246, LE250, LE252, LE253, LE322, LE360, LE361, LE456, LE670, LY32Y, LY36Y, LY200, LY214, LY250, LY252, LY253, LY322, LY324, LY360, LY362,

ERRATA

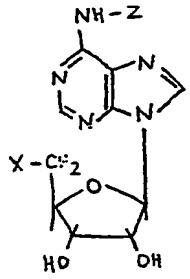
SPECIFICATION No. 1,101,108

Page 2, line 105, *after* "tosyl" *delete* "O"
Page 3, line 53, *for* "least" *read* "lowest"
Page 4, line 26, *for* "methyl" *read* "allyl"

THE PATENT OFFICE
17th April 1968



(I)



(II)

wherein R is a saturated or unsaturated, straight or branched-chain aliphatic hydrocarbon radical and X is a halogen atom, an azido group or an alkylmercapto radical.

The new adenosine derivatives according to the present invention, on the one hand, dilate the peripheral blood vessels of the circulatory

in which X has the same meaning as above and Z is a hydrogen atom or a formyl radical, or the 2',3' - *o* - isopropylidene derivatives thereof, with an N - alkylation or N - alkenylation agent, followed, if necessary, by the removal of protective groups by acid hydrolysis; or by the reaction of compounds of the general formula: —

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Int. Cl.:—C 07 d 5/04, C 07 d 57/64

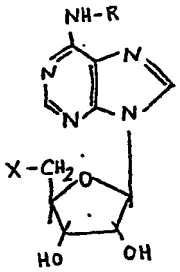
COMPLETE SPECIFICATION

Disubstituted Adenosine Derivatives

We, C. F. BOEHRINGER & SOEHNE G.m.b.H., of Mannheim-Waldhof, Germany, a Body Corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new disubstituted adenosine derivatives and with the preparation thereof.

The new adenosine derivatives according to the present invention are compounds of the general formula:—

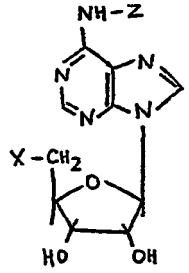


(I)

wherein R is a saturated or unsaturated, straight or branched-chain aliphatic hydrocarbon radical and X is a halogen atom, an azido group or an alkylmercapto radical.

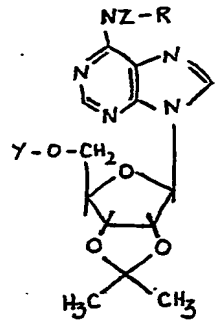
The new adenosine derivatives according to the present invention, on the one hand, dilate the peripheral blood vessels of the circulatory system and, on the other hand, suppress the cardiac activity by slowing down the heart rate. According to which properties are the most strongly marked, the new compounds according to the present invention are suitable for the reduction of blood pressure in high blood pressure diseases, especially in cases of secondary heart strain, or for dilation of the blood vessels and increase of the peripheral blood flow in the case of diseases of the blood vessels.

The preparation of the new compounds according to the present invention takes place in known manner either by the reaction of compounds of the general formula:—



(II)

in which X has the same meaning as above and Z is a hydrogen atom or a formyl radical, or the 2',3' - o - isopropylidene derivatives thereof, with an N - alkylation or N - alkenylation agent, followed, if necessary, by the removal of protective groups by acid hydrolysis; or by the reaction of compounds of the general formula:—



(III)

in which R and Z have the same meanings as above and Y is the residue of a sulphonic acid, with an alkali metal compound of the general formula Me . X (IV), in which X has the same meaning as above and Me is an alkali metal atom, whereafter the protective groups are split off by acid hydrolysis.

As N - alkylation or N - alkenylation agents there can be used all the usual reactive alkyl and alkenyl derivatives with which it is possible to carry out an N - alkylation or N - alkenylation of the sensitive adenosine molecule without decomposition occurring. The corresponding alkyl or alkenyl iodides of the general formula RI, in the presence of barium hydroxide, have proved to be especially useful. For the preparation of hydroxyalkyl derivatives, however, the corresponding epoxides are also suitable.

The formyl derivatives of (II) and (III) have, in comparison with the compounds in which Z is a hydrogen atom, proved to be especially useful since, when they are used as starting materials, there are obtained particularly good yields of very pure products. In some cases, for example in the case of the preparation of 5' - alkylmercapto compounds from compounds of general formula (III) with the use of alkyl mercaptides, good results can be obtained when starting with compounds of general formula (III) in which Z is a hydrogen atom.

The preferred sulphonic acid residue Y in the compounds (III) is the tosyl radical.

The splitting off of the protective groups, namely, of the isopropylidene groups and possibly of the formyl groups, takes place simultaneously with the use of dilute acids, preferably at room temperature.

The following Examples are given for the purpose of illustrating the present invention:—

EXAMPLE 1.

N(6) - propyl - 5' - desoxy - 5' - azido - adenosine.

10 g. N(6) - formyl - 2',3' - O - isopropylidene - 5' - desoxy - 5' - azido - adenosine (prepared in the manner described by W. Jahn, Chem. Ber., *98*, 1705/1965) are dissolved in 150 ml. dimethyl formamide and mixed with a mixture of 50 g. barium oxide and 1.5 g. barium hydroxide octahydrate. 30 ml. propyl iodide are added thereto and the reaction mixture stirred overnight. The reaction mixture is then diluted with chloroform, centrifuged and the chloroform solution decanted off and then washed with water. The residue is dissolved in 30 ml. formic acid and mixed with an equal volume of water. This is then left to stand for 4 days and thereafter neutralised with an aqueous solution of ammonia. The precipitate obtained is filtered off with suction and recrystallised from water with the use of activated charcoal. There are obtained 5.1 g. (48% of theory) N(6) - propyl - 5' - desoxy - 5' - azido - adenosine with a melting point of 112—113°C.

EXAMPLE 2

N(6) - propyl - 5' - desoxy - 5' - chloro-adenosine.

The N(6) - formyl - 2',3' - O - isopropylidene - 5' - chloro - adenosine obtainable from 5 g. N(6) - formyl - 2',3' - O - isopropylidene - 5' - O - tosyl - adenosine (c.f. W. Jahn Chem. Ber., *98*, 1705/1965) is dissolved in 50 ml. dimethyl formamide and, after the addition of 25 g. barium oxide and 0.7 g. barium hydroxide octahydrate, mixed with 12 ml. *n*-propyl iodide. The reaction mixture is stirred for 18 hours at room temperature, about 100 ml. chloroform are then added thereto, centrifuged and the chloroform solution decanted off. After shaking out with an aqueous thiosulphate solution and with water, the chloroform solution is evaporated and the isopropylidene group saponified with dilute formic acid in the manner described in Example 1. There are obtained 1.2 g. (28% of theory) N(6) - propyl - 5' - desoxy - 5' - chloroadenosine with a melting point of 104—108°C.

In an analogous manner but using *n*-butyl iodide and *n*-hexyl iodide instead of *n*-propyl iodide, there are obtained N(6) - *n* - butyl - 5' - desoxy - 5' - chloroadenosine of melting point 90—93°C. and N(6) - *n* - hexyl - 5' - desoxy - 5' - chloroadenosine of melting point 78—80°C., respectively.

EXAMPLE 3.

N(6) - allyl - 5' - desoxy - 5' - chloro-adenosine.

Approximately 14 g. crude 2',3' - O - isopropylidene - N(6) - allyl - 5' - O - tosyl O - adenosine (which was prepared in the manner described below by the tosylation of 2',3' - O - isopropylidene - N(6) - allyl - adenosine) are dissolved in 85 ml. formic acid - acetic acid anhydride (prepared from equivalent amounts of formic acid and acetic

anhydride in the manner described by K. Freudenberg and W. Jakob, Chem. Ber., *80*, 326/1947) and left to stand for one day at room temperature. The reaction mixture is then evaporated in a vacuum and the residue dissolved in 100 ml. dimethyl sulphoxide, 9 g. lithium chloride added thereto and the reaction mixture heated on a steam bath for 20 minutes. The reaction mixture is then mixed with water and extracted with chloroform. The chloroform solution is evaporated and the residue dissolved in 50 ml. formic acid. Water is then added until the commencement of cloudiness and the mixture then left to stand for 4 days. This solution is then neutralised with a concentrated aqueous solution of ammonia. The resultant precipitate is filtered off with suction and then recrystallised from methanol. There are obtained 3.7 g. (35% of theory) N(6) - allyl - 5′ - desoxy - 5′ - chloroadenosine with a melting point of 143—146°C.

The 2′,3′ - O - isopropylidene - N(6) - allyl - 5′ - O - tosyl - adenosine used as starting material is prepared in the following manner:

10 g. 2′,3′ - O - isopropylidene - adenosine are slurried in 100 ml. dimethyl formamide and 30 ml. allyl iodide and stirred for 5 hours. The reaction mixture is then left to stand for 8 hours and thereafter the red-brown reaction mixture is decolorised with a concentrated solution of sodium bisulphite. 100 ml. 2N sodium hydroxide solution are added to the pale yellow solution and the reaction mixture heated to boiling for 25 minutes. After cooling, it is extracted with chloroform. The residue obtained by evaporation of the chloroform extract consists of 9.1 g. 2′,3′ - O - isopropylidene - N(6) - allyl - adenosine in the form of a yellow syrup. This syrup is dissolved in 60 ml. anhydrous pyridine, the solution cooled to −20°C. and 10 g. *p* - toluene - sulphonyl chloride then added thereto. The mixture is then allowed to stand, with occasional shaking, for 18 hours at −20°C. Water is then added and the mixture shaken out with chloroform. The chloroform phase is shaken out with ice-cooled 2N sulphuric acid for removal of pyridine. Thereafter it is washed with water and, after drying over anhydrous sodium sulphate, the chloroform solution is evaporated in a vacuum at the least possible temperature. The yield of crude 2′,3′ - O - isopropylidene - N(6) - allyl - 5′ - O - tosyl - adenosine is about 14 g. and it can be used directly for further reaction.

The following compounds are prepared in an analogous manner:

N(6) - methyl - 5′ - desoxy - 5′ - chloroadenosine of melting point 157—158°C. in a yield of 30% of theory;

N(6) - methallyl - 5′ - desoxy - 5′ - chloroadenosine of melting point 129—131°C. in a yield of 40% of theory;

N(6) - ethyl - 5′ - desoxy - 5′ - chloroadenosine of melting point 153—155°C. in a yield of 25% of theory; and

N(6) - isobutyl - 5′ - desoxy - 5′ - chloroadenosine of melting point. 70°C. in a yield of 34% of theory.

Example 4.

N(6) - allyl - 5′ - desoxy - 5′ - azido - adenosine.

Crude 2′,3′ - O - isopropylidene - N(6) - allyl - N(6) - formyl - 5′ - O - tosyl - adenosine (c.f. Example 3) is dissolved in 100 ml. dimethyl sulphoxide. 9 g. sodium azide are then added to the solution which is thereafter heated on a steam bath for 15 minutes. The reaction mixture is then diluted with water and shaken out with chloroform. After washing with water, the chloroform solution is dried and evaporated. The residue is saponified with dilute formic acid in the manner described in Example 2. There are thus obtained 2.2 g. (20% of theory) N(6) - allyl - 5′ - desoxy - 5′ - azido - adenosine with a melting point of 90—92°C.

Example 5.

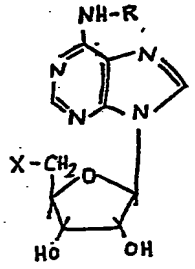
N(6) - allyl - 5′ - desoxy - 5′ - methylmercapto - adenosine.

Crude 2′,3′ - O - isopropylidene - N(6) - allyl - 5′ - O - tosyl - adenosine (c.f. Example 3) is added portionwise to a solution of sodium methyl mercaptide (prepared from 1.4 g. sodium and 3 g. methyl mercaptan) in 100 ml. liquid ammonia. The reaction mixture is stirred for 4 hours and the ammonia then allowed to evaporate. After the addition of 1 g. ammonium chloride, the reaction mixture is extracted with choloroform. The evaporation residue from the chloroform solution is dissolved in 1N sulphuric acid and left to stand for 3 days. It is then neutralised with a concentrated solution of ammonia and, after a few hours, the precipitate obtained filtered off with suction. There are obtained 4.4 g. (40% of theory) N(6) - allyl - 5′ - desoxy - 5′ - methylmercapto - adenosine.

In an analogous manner but starting from 2′,3′ - O - isopropylidene - N(6) - methyl - 5′ - O - tosyl - adenosine (c.f. Example 3), there is obtained N(6) - methyl - 5′ - desoxy - 5′ - methyl - mercapto - adenosine with a melting point of 173—175°C.

WHAT WE CLAIM IS:—

1. Adenosine derivatives of the general formula:—



wherein R is a saturated or unsaturated, straight or branched-chain aliphatic hydrocarbon radical and X is a halogen atom, an azido group or an alkylmercapto radical.

2. N(6) - propyl - 5' - desoxy - 5' - azido - adenosine.

3. N(6) - propyl - 5' - desoxy - 5' - chloroadenosine.

4. N(6) - *n* - butyl - 5' - desoxy - 5' - chloroadenosine.

5. N(6) - *n* - hexyl - 5' - desoxy - 5' - chloroadenosine.

6. N(6) - allyl - 5' - desoxy - 5' - chloroadenosine.

7. N(6) - methyl - 5' - desoxy - 5' - chloroadenosine.

8. N(6) - methallyl - 5' - desoxy - 5' - chloroadenosine.

9. N(6) - ethyl - 5' - desoxy - 5' - chloroadenosine.

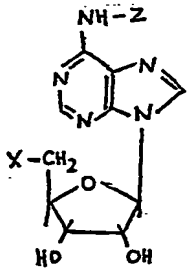
10. N(6) - isobutyl - 5' - desoxy - 5' - chloroadenosine.

11. N(6) - allyl - 5' - desoxy - 5' - azido - adenosine.

12. N(6) - methyl - 5' - desoxy - 5' - methylmercapto - adenosine.

13. N(6) - methyl - 5' - desoxy - 5' - methylmercapto - adenosine.

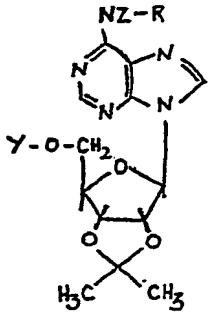
14. Process for the preparation of adenosine derivatives of the general formula given in claim 1, wherein a compound of the general formula:—



in which X has the same meaning as in claim 1 and Z is a hydrogen atom or a formyl radical, or the 2',3' - O - isopropylidene derivative thereof, is reacted with an N-alkylation or N-alkenylation agent and thereafter, if necessary, the protective groups split off by acid hydrolysis.

15. Process according to claim 14, wherein the N-alkylation or N-alkenylation agent is a compound of the general formula RI, R having the same meaning as in claim 1, the reaction being carried out in the presence of barium hydroxide.

16. Process for the preparation of compounds of the general formula given in claim 1, wherein a compound of the general formula:—



in which R has the same meaning as in claim 1, Z is a hydrogen atom or a formyl radical and Y is the residue of a sulphonic acid, is reacted with an alkali metal compound of the general formula Me . X, in which X has the same meaning as in claim 1 and Me is an alkali metal atom, whereafter the protective groups are split off by acid hydrolysis.

17. Process according to claim 16, wherein the sulphonic acid residue Y is a tosyl radical.

18. Process for the preparation of compounds of the general formula given in claim 1, substantially as hereinbefore described and exemplified.

19. Compounds of the general formula given in claim 1, whenever prepared by the process according to any of claims 14 to 18.

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Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1968.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

App. No. 10/608,689
Filed: June 27, 2003
Inventor: BIGOT, et al.
Docket No. DEAV2002/0059 US NP
PRIOR ART